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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,064	01/12/2005	Dierk Wieckhusen	PN4-32593A	6846

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ONE HEALTH PLAZA 104/3
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EXAMINER	
KARPINSKI, LUKE E	
ART UNIT	**PAPER NUMBER**
4173	

MAIL DATE	DELIVERY MODE
10/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,064	WIECKHUSEN ET AL.	
	Examiner	Art Unit	
	Luke E. Karpinski	4173	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) *3-5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 pages*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

1. Claims 3-5 are objected to because of the following informalities: None of Claims 3-5 ends with a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant claims that the crystals may be in several different forms but Applicant has not adequately described how one skilled in the art could obtain crystals in said forms. It is known in the art that the existence of polymorphic forms is unpredictable and the mere allegation of having all polymorphic forms is unpersuasive.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 1, 2, 7, 8, and 22-25 are rejected under 35 U.S.C. 112, second paragraph. The term "X_{50} value" in claims 1, 2, 7, 8, and 22-25 is an unclear term, which renders the claim indefinite. The term " X_{50} value" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. There is no definition of the term " X_{50} value" and therefore it cannot be determined what type of size range Applicant is claiming.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, and 6-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mutlib et al. and US Publication No. US 2002/0045582 A1 to Margolin et al.

Applicant Claims

Applicant claims an injectable depot formulation comprising crystals of iloperidone or related structures of a specified size range and of different shapes. Applicant also claims said formulation comprising a suitable vehicle as well as excipients well known in the art.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Mutlib et al. teaches the iloperidone structures (introduction) in claim 2 of the instant application for use as a pharmaceutical compound.

Margolin et al. teaches the use of crystals as advantageous for pharmaceutical dosage formulations (paragraph 28) and the administration of crystal formulations through modes such as, parenteral, subcutaneous, and intravenous (paragraph 82). Margolin et al. also teaches that crystals are used for slow-release formulations and that the size and shape of the crystals are important to the dissolution of the crystals and the release of activity (paragraph 28 and 29). Further, Margolin et al. teaches the common excipients and additives that may be added to an injectable crystalline suspension (paragraphs 88(excipients), 102(preservatives), 111(coating agents), 112(sodium carboxymethylcellulose), 119(emulsifiers/solubilizers), 120(stabilizer), 127(humectants), 128(propylene glycol), 131(plasticizers), 132(polyethylene glycol), 135(solvents), 136(propylene glycol), 145(suspending/viscosity agents), 146(carboxymethylcellulose sodium), 147(sweetening agents), 148(mannitol), 150(sodium carboxymethylcellulose), 152(mannitol), 157(tonicity agent), 158(mannitol), and 170(wetting/solubilizing agent)).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Mutlib et al. does not teach injectable iloperidone formulations, nor does Mutlib et al. teach the excipients that are claimed in the instant application. Margolin et al. cures the deficiencies of the teaching of Matlib et al. by teaching the common use of crystal structures as well as the claimed excipients in injectable solutions.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

At the time of the invention iloperidone compounds for pharmaceutical use were well known in the art. At the time of the invention it was also well known that pharmaceutical formulations in the crystalline form were advantageous to use and that by changing the size or shape of the crystal the dissolution and active ingredient release could be modified. Although Margolin et al. focuses on crystalline forms of proteins, the general properties of crystals vs. amorphous forms would be expected to be the same for protein and small molecule crystals. It was also known that any common excipients and additives could be added to the injectable crystalline suspension. It is an inherent property of the claimed compound that it can be crystallized. Using the preceding logic, it would have been obvious at the time of the invention to one of ordinary skill in the art to crystallize the iloperidone compound and administer it to patients as an injectable depot formulation. Mutlib et al., with the teachings of Margolin et al., make obvious all of the structures disclosed in the instant claims 1 and 2, the references also make obvious the use of crystals of these structures within an injectable depot formulation, the use of water as a suspension vehicle, adding any excipients known in the art, and using any other form of the drug, such as, salts and hydrates.

In regards to the claim limitation of a size range of the crystals and of different crystal forms, changing the size is simply seen as routine optimization to modify the release of the active compound.

In regards to the claim limitation of having a concentration range, this is simply seen as routine optimization and is well known in the art.

In regards to the claim limitation of dosage, this is simply seen as routine optimization and is well known in the art.

For these reasons a person of ordinary skill in the art would have a reasonable expectation of success upon modification of the teachings of Mutlib et al. with the teachings of Margolin et al. to use the crystalline form of iloperidone in an injectable solution.

Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mutlib et al. and US Publication No. US 2002/0045582 A1 to Margolin et al., in further view of Corey et al.

Applicant Claims

Applicant claims a depot formulation of two separate stereoisomers of the claimed compound as well as a combination of the stereoisomers.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Mutlib et al. teaches the iloperidone structures (introduction) in claim 2 of the instant application for use as a pharmaceutical compound.

Corey et al. teaches enatioselective reduction of ketones.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Mutlib et al. does not teach enantioselective variations of iloperidone structure nor does it teach the crystalline form of the compound. Mutlib et al. also does not teach injectable iloperidone formulations.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

Corey et al. cures the deficiencies of the teaching of Matlib et al. by teaching the enantioselective reduction of ketones. At the time of the invention iloperidone compounds for pharmaceutical use were well known in the art. It was also well known in the art that enantioselective reduction of ketones could be performed. It would have been obvious to one of ordinary skill in the art to use this simple enantioselective ketone reduction to synthesize compounds II and III as described in claims 3-5 of the instant application. The ordinary skilled artisan would have been capable of obtaining either or both claimed enantiomers per the teachings of Corey et al. A person of ordinary skill in the art would have a reasonable expectation of success of synthesizing both of the enantiomers. Thus, claims 3-5 are found prima facie obvious over the combined teachings of Matlib et al. and Corey et al. The combined teachings of Matlib et al. and Corey et al. make obvious the enatiomers of claims 3 and 4 either together or separate, in crystalline form for use in an injectable depot formulation.

Inquiries

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Luke E. Karpinski whose telephone number is 571-270-3501. The examiner can normally be reached on Monday Thursday 9-4 est.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Ardin H. Marschel or Cecilia Tsang can be reached on 571-272-0718 or 571-272-0562 respectively. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ardin H Marschel 10/10/07

LEK

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER